Remarks

Claims 1-21 are pending. Claims 1, 10 and 12-19 have been amended. Support for the amendment to claims 1 and 10 can be found, for example, in Examples 1-7 (transforming cells with genes encoding diol oxidoreductase and aldehyde dehydrogenase); and, in particular, Example 4 and Example 6. Claims 12-19 have been amended to properly depend from claim 11.

The present invention is directed to methods of generating a range of 4HB copolymers and poly-4HB homopolymers using cells transformed with genes encoding the enzymes diol oxidoreductase and aldehyde dehydrogenase. Once transformed, the cells utilize these enzymes, *inter alia*, to convert 1,4-butanediol substrate to 4HB monomer.

Rejection Under 35 U.S.C. § 102

Claims 1, 4 and 8-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 98/39435 by Hein *et al.* ("Hein"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner has stated that the genetically modified organisms of Hein "naturally express aldH and dhaT genes." The Examiner further points to pages 3 and 4 for a teaching of PHA synthase expression and "a 1,4-butanediol". However, the applicant's have reviewed the cited pages and have not found any reference to a 1,4-butanediol. Furthermore, the applicants respectfully submit that the claims, as presently amended, require one to introduce the genes encoding diol oxidoreductase and aldehyde dehydrogenase for the conversion of diols to hydroxyalkanoate monomers. Because the ***introduction*** of genes encoding diol oxidoreductase

and aldehyde dehydrogenase are necessary for the described conversion, these genes are not naturally expressed.

Claims 1, 5 and 8-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by *Appl. Microbiol. Biotechnol.* (1995) 42:901-909, by Lee *et al.* ("Lee"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Lee teaches the use of aerobic bacteria for the production of a complex copolyester containing 3-hydroxybutyric acid (3HB) from 3-hydroxybutyric acid or from 1,3-butanediol under nitrogen-limited culture conditions. The applicants respectfully submit that Lee fails to provide any teaching related to the *introduction* of genes encoding diol oxidoreductase and aldehyde dehydrogenase for the conversion of diols to hydroxyalkanoate monomers. While heterologous gene expression is taught in Lee, it *refers only to the expression of polyhydroxyalkanoate synthase* from *Pseudomonas* sp. A33.

Claims 1, 5, 7-8 and 10 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,329,183 to Skraly *et al.* ("Skraly 1"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Skraly 1

Skraly 1 teaches production of poly (3-hydroxyalkanoate) homopolymers or co-polymers incorporating 3-hydroxypropionate or 3-hydroxyvalerate monomers wherein the units are derived from the enzyme catalysed conversion of diols. The suitable diols disclosed are: 1,2-propanediol, 1,3-propanediol, and glycerol.

Skraly 1 fails to teach **diol oxidoreductase** and aldehyde dehydrogenase, wherein diol oxidoreductase and aldehyde dehydrogenase convert the 1,4 butanediol into hydroxyalkanoate monomers. More specifically, there is no teaching of methods for the production of PHAs containing 4HB monomer. As briefly explained in the background of the present invention, the production of a range of 4HB copolymers and poly-4HB homopolymer, for example, using 1,4-butanediol as the "initiating" source is highly advantageous. The two enzymes, diol oxidoreductase and aldehyde dehydrogenase, convert 1,4 butanediol to 4-hydroxybutyraldehyde (*via* diol oxidoreductase) and 4-hydroxybutyraldehyde to 4-hydroxybutyrate (*via* hydroxybutyrate).

Claims 1, 5, 7-8 and 10 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S.S.N. 09/944,243 by Skraly *et al.* ("Skraly 2"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Skraly 2

Skraly 2 teaches that genes encoding a vicinal diol dehydratase, from an organism that naturally can convert glycerol to 3-hydroxypropionaldehyde, may be introduced into the genetically altered host cell. Skraly further describes suitable diols that may be used to feed the host include 1,2-propanediol, 1,3 propanediol and glycerol.

Skraly 2 fails to teach **diol oxidoreductase** and aldehyde dehydrogenase, wherein diol oxidoreductase and aldehyde dehydrogenase convert the 1,4 butanediol into hydroxyalkanoate monomers. More specifically, there is no teaching of methods for the production of PHAs

containing 4HB monomer. As briefly explained i the background of the invention, the production of a range of 4HB copolymers and pol -4HB homopolymer, for example, using 1,4-butanediol as the "initiating" source, is highly adv ntageous. The two enzymes, diol oxidoreductase and aldehyde dehydrogenase, take 1,4 butanediol to 4-hydroxybutyraldehyde (*via* diol oxidoreductase) and 4-hydroxybutyraldehyde to 4-hydroxybutyrate (*via* hydroxybutyrate).

Rejection Under 35 U.S.C. § 103

Claims 1-3 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/39453 by Hein *et al.* ("Hein") in view of CAPLUS abstract by Doi *et al.* ("Doi"). Applicants respectfully traverse this rejection to the extent th it it is applied to the claims as amended.

Doi

Doi describes three different types of biodegradable copolyesters that were produced from various C substrates in a batch culture of *A. eutrophus*. The random co-polymer 3-hydroxybutyrate and 3-hydroxypropionate was produced in a N-free culture of 3-hydroxypropionic acid, 1,5-pentanediol, 1,7-heptanediol, or 1,9-nonanediol. The co-polyester of 3-hydroxybutyrate and 4-hydroxybutyrate, P(HB co-4HB), was produced from various C sources such as 4-hydroxybutyric acid, γ-butyrolactone, 1,4-butanediol, 1,6-hexanediol, 1,8-octanediol, 1,10-decanediol, and 1,12-dodecanediol. Doi does not disclose the use of a ***diol feedstock or pathways*** for the conversion of a diol into a PHA monomer such as 4HB etc.

Hein

The Hein reference teaches the ***natural*** expression of the aldH and dhaT genes (i.e. e pression of endogenous aldH and dhaT genes). As descri ed above, the applicants r spectfully submit that the claims, as presently amended, re uire one to introduce the genes e coding diol oxidoreductase and aldehyde dehydrogenase f r the conversion of diols to h ydroxyalkanoate monomers. Because the ***introduction*** of g enes encoding diol oxidoreductase a nd aldehyde dehydrogenase are necessary for the described conversion, these genes are not n aturally expressed. None of the examples in Hein describe even the use of 1,4-butanediol as a p recursor for 4HB polymers. There is no mention or teachi g in Hein regarding aldH and dhaT g enes or the desirability of genetically engineering these ge es to produce PHA polymers from d iols.

Summary

Neither of the references, singly or in combination, t each the ***introduction*** of genes e ncoding diol oxidoreductase and aldehyde dehydrogenase.

Claims 1-2 and 6-7 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Appl. Microbiol. Biotechnol.*, 42:901-909, by Lee *et al.* ("L e"), in view of WO 99/64617 by Asrar *et al.* ("Asrar"). Applicants respectfully traverse this rejection to the extent that it is a pplied to the claims as amended.

Lee

Lee teaches the use of aerobic bacteria for the prod ction of a complex copolyester c ontaining 3-hydroxybutyric acid (3HB) from 3-hydroxyb tyric acid or from 1,3-butanediol

under nitrogen-limited culture conditions. The applicants respectfully submit that Lee fails to provide any teaching related to the *introduction* of genes encoding diol oxidoreductase and aldehyde dehydrogenase for the conversion of diols to hydroxyalkanoate monomers. Heterologous gene expression is taught in Lee; *referring only to the expression of polyhydroxyalkanoate synthase* from *Pseudomonas* sp. A33. Lee is completely silent on genetically engineering organisms to express a diol oxidoreductase and/or an aldehyde dehydrogenase which functions to enable or enhance the conversion of diol feedstocks to the corresponding hydroxyacids which are then incorporated into the PHA copolymers.

Asrar

Asrar teaches a method of making hydroxy-terminated PHA in a PHA-producing microorganism by cultivating the microorganism in the presence of an aliphatic diol or an aliphatic polyol. Asrar incorporates an aliphatic diol or polyol onto the end of the growing PHA polymer chain by a transesterification reaction such that the end groups obtained are primary hydroxyl groups. The PHA polymers thus obtained have 50% of the total end groups comprising secondary alcohols from the normal end units of the PHA chain and additional hydroxyl-end groups comprising primary alcohols obtained by the transesterification reaction such that the total end group hydroxyl content is greater than 50%. Asrar is silent on the use of organisms, which have been genetically engineered to express a diol oxidoreductase and/or an aldehyde dehydrogenase as a means to improve the production of PHA copolymers based on diol feedstocks wherein the diol oxidoreductase and/or aldehyde dehydrogenase function to enhance

the conversion of the diols to the corresponding hydroxyacids which are then incorporated into the PHA.

Summary

Neither of the references, singly or in combination, teach the ***introduction*** of genes encoding diol oxidoreductase and aldehyde dehydrogenase.

Claims 1-2 and 6-7 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/19453 by Hein *et al.* ("Hein") in view of WO 99/64617 by Asrar *et al.* ("Asrar"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Hein

The Hein reference teaches the ***natural*** expression of the aldH and dhaT genes (i.e. expression of endogenous aldH and dhaT genes). As described above, the applicants respectfully submit that the claims, as presently amended, require one to introduce the genes encoding diol oxidoreductase and aldehyde dehydrogenase for the conversion of diols to hydroxyalkanoate monomers. Because the ***introduction*** of genes encoding diol oxidoreductase and aldehyde dehydrogenase are necessary for the described conversion, these genes are not naturally expressed. Also, please see foregoing arguments under 35 U.S.C. 103.

Asrar

Asrar teaches a method of making hydroxy-terminated PHA in a PHA-producing microorganism by cultivating the microorganism in the presence of an aliphatic diol or an aliphatic polyol. Also. please see foregoing arguments under 35 U.S.C. 103.

Summary

Neither of the references, singly or in combination, teach the ***introduction*** of genes encoding diol oxidoreductase and aldehyde dehydrogenase.

Double Patenting Rejection

Claims 1, 5, 7-8 and 10 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,329,183. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed in the foregoing sections, the applicants have amended the claims to rely upon the organisms being transformed with genes encoding diol oxidoreductase and aldehyde dehydrogenase, wherein diol oxidoreductase and aldehyde dehydrogenase convert 1,4 butanediol into hydroxyalkanoate monomers. There is nothing in U.S. Patent No. 6,329,183 to suggest the transformation of cells with genes encoding diol oxidoreductase and aldehyde dehydrogenase so that the cells may drive the formation of hydroxyalkanoate monomers *via* 1,4 butanediol.

Claims 1, 5, 7-8 and 10 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of co-pending

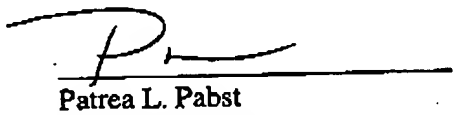
U.S.S.N. 09/909,574
Filed: July 20, 2001
AMENDMENT AND RESPONSE TO OFFICE ACTION

Application Serial No. 09/944,243. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed in the foregoing sections, the applicants have amended the claims to rely upon the organisms being transformed with genes encoding diol oxidoreductase and aldehyde dehydrogenase, wherein diol oxidoreductase and aldehyde dehydrogenase convert 1,4 butanediol into hydroxyalkanoate monomers. There is nothing in Application Serial No. 09/944,243 to suggest the transformation of cells with genes encoding diol oxidoreductase and aldehyde dehydrogenase so that the cells may drive the formation of hydroxyalkanoate monomers *via* 1,4 butanediol.

Allowance of claims 1-21 is respectfully solicited.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: July 28, 2003

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)